International Journal of Pharmaceutics, 77 (1991) 183–191

IJP 02568

Preparation of coated particles using a spray drying process with an aqueous system

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(Received 12 April 1991)
(Modified version received 24 June 1991)
(Accepted 26 June 1991)

Key words: Spray drying; Aqueous coating; Flow properties; Theophylline; Hydroxypropylmethylcellulose; Dissolution

Summary

Coated theophylline particles were prepared by a spray-drying process. The process was carried out using an aqueous solution of hydroxypropylmethylcellulose as the coating polymer. The effects of spray nozzle size, inlet drying temperature, drying air flow rate, feed spray rate and atomizing pressure were studied. The flow properties of the spray-dried particles improved with decrease in the air-to-liquid diameter ratio of the nozzle and increase in the inlet temperature. A high inlet drying temperature produced coated particles with a slower drug dissolution rate. The particles that had been spray dried at a faster drying air flow rate were found to have better flowability, as indicated by lower values of Kawakita's constants, a and $1/b$, Hausner ratio and Carr index, and longer dissolution $T_{50\%}$ values. High feed spray rates resulted in ineffective atomization, producing badly formed spray-dried products. Atomizing pressure affected only the particle size of the product formed. The smaller particles had a higher dissolution $T_{50\%}$ and were more cohesive.

Introduction

Spray-drying techniques have been widely used in the pharmaceutical, chemical and food industries mainly for the drying of substances. However, other applications in the pharmaceutical industries include the drying of heat-sensitive materials (Newton, 1966), improving the solubility of poorly water-soluble substances (Kawashima et al., 1975), preparing granulations for tabletting (Raff et al., 1961) and coating drugs with suitable polymers to produce dust-free powders (Seagar, 1977). Normal encapsulation techniques frequently require the formation of a core, followed by a coating process. Spray-drying techniques may prove to be more useful for the preparation of microcapsules because the coated particles can be produced directly from droplets in a single process (Takenaka et al., 1980). In addition, spray-dried products are known to have improved flow properties, thus increasing the ease of incorporation into a dosage form.

An attempt was therefore made to investigate the potential use of a spray-drying technique as an alternative to conventional microencapsula-

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tion methods for preparing coated drug particles. As the use of organic solvents incurs risks of toxicity and explosions, aqueous systems are becoming increasingly popular (Takeuchi et al., 1989). The primary objective of this study was to produce theophylline particles coated with a cellulose polymer, hydroxypropylmethylcellulose, by spray drying using an aqueous system. However, as in every technique, it is imperative that the selection and optimization of methodology, choice of coating materials, plasticizer and other pharmaceutical ancillaries undergo a critical examination in order to obtain a suitable coating, yield, size and size distribution, flowability and dissolution properties. Although spray drying has been studied and evaluated for the process of drying, there is little detailed discussion as yet as to how the operating controls can affect the formation of coated products in the aqueous system.

Materials and Methods

The drug used was anhydrous theophylline (B.P. Grade, China). Coating agent, hydroxypropylmethylcellulose (HPMC, Shin-Etsu Chemical, Japan), has a viscosity of 52.2 cps (2% w/v solution) at 20°C.

Spray-drying technique

The polymer (1.25% w/v) and the drug (0.25% w/v) were wetted with some water until both the drug and polymer were in solution and made up to 500 ml. The resultant solution was then spray dried using a laboratory spray dryer (Pulvis Minispray GA32, Yamato Scientific, Japan) with the following dimensions: width, 760 mm; length, 420 mm; height, 1350 mm. A 2-fluid pressure nozzle with a cone-shaped spray pattern of angle 18–20° emerging from the nozzle orifice was used. The atomised droplets produced were no larger than than 100 μm. The flow type was co-current with internal mixing of air and liquid with the nozzle head. The feed spray rate was 9 ml/min. The product was collected in a cyclone separator.

Dissolution studies

The rate of release of theophylline from the spray-dried products was determined using a dissolution apparatus (Method 1, USPXXI, Model 72RL, Hanson Research, U.S.A.) with the base of the rotating basket lined with a circular plastic disc to retain the powder. The basket was rotated at 50 rpm. The dissolution medium was 900 ml deaerated distilled water maintained at 37 ± 0.5°C. 4-ml samples were withdrawn at specified intervals over 4 h using an automated sampler (Dissoette, Model 27-6A, Hanson Research, U.S.A.). The amount of theophylline was determined spectrophotometrically at 274 nm (HP 8451A, Hewlett Packard, U.S.A.). At least three replicates were carried out for each batch of product and the results averaged.

Moisture content

Approx. 300 mg of the powder was weighed and the moisture content determined using an electronic moisture balance (EB330MOC, Shimadzu, Japan) at 80°C.

Mean particle volume

The mean particle volume was calculated using the mean equivalent spherical diameter (E.S. diameter). The E.S. diameter was determined using a computerized video image analysis system (Imageplus, Dapple System, U.S.A.) attached to a microscope. The E.S. diameter was derived from the values of at least 200 particles for each batch:

$$\text{E.S. diameter} = (\text{breadth})^{2/3} \times (\text{length})^{1/3}$$

$$\text{Particle Volume} = \pi(\text{E.S. diameter})^3/6$$

Flow properties

The determination of flowability was carried out in a humidity-controlled environment with a relative humidity of 50–60%. Kawakita's constants, a and $1/b$, were obtained by a method modified from Yamashiro et al. (1983) with a 10 ml measuring cylinder. The change in volume was measured after every 2 taps for 40 taps. The constants, a and $1/b$, are related to compactibility or fluidity and cohesion, respectively, in Kawakita's equation.

$$N/C = (1/a)N + 1/ab$$

where N is the number of taps, $C = (V_0 - V_n)/V_0$ represents the degree of volume reduction, V_0 is the initial volume and V_n denotes the bulk volume which was measured at every 2 taps. Kawakita's constants obtained were the mean values of four replicates.

The Hausner ratio is a measure of the interparticulate friction and can be used to predict powder flowability. A higher value indicates greater cohesion between particles. A high Carr index value is indicative of the tendency to bridging. The method used to determine the Hausner ratio and Carr index was similar to that described by Wan and Lim (1988). The product was tapped for 1000 taps in a filled 10 ml cylinder. An average of four determinations was taken.

Results and Discussion

The product properties may be governed by spray nozzle size, inlet drying temperature, drying air flow rate, feed spray rate and atomizing pressure. Each of these variables can affect particle size and size distribution, bulk density, moisture content and drug crystal form.

Spray-dried particles are generally not of the matrix type. They are usually hollow spheres. In the process of drying, two possible types of products may be formed. If the drug crystallises out within the polymeric solution, then it would be subsequently coated by the polymer. The other possibility would be the solidification of the polymer first, causing the enclosed drug to be drawn to the surface, resulting in drug crystal protrusions on the polymeric surface. Preliminary X-ray diffraction measurements have shown that the drug present is in crystalline form. Therefore, the drug cannot be in a solid dispersion with the polymer. Evidence of the drug being coated by the polymer can be seen later by (a) the delayed dissolution and (b) the existence of a film over the crystal surface noted under SEM.

Spray nozzle size

Five different nozzle sizes were used. Comparison between the products showed that the air-to-liquid ratio affected the product particle size. Changes in particle size, in turn, influence the flowability. Smaller sized products are more cohesive and do not flow well. The dissolution profiles were similar for the products obtained when spray dried with the various nozzle sizes (Wan et al., 1990).

Inlet drying temperature

Among the four drying temperatures, 100, 120, 150 and 170°C studied, 150°C appeared to be most suitable for the preparation of the microcapsules. A high inlet temperature gave rise to products which were larger and had lower moisture content. Both factors contributed to an improved flowability while the larger particles resulted in slower dissolution (Wan et al., 1990).

Drying air flow rate

The flow rate of drying air can be varied from 0.4 to 0.6 m^3/min. When the flow rate was less than 0.4 m^3/min, the product was not completely dried. It was sticky and could not be removed from the collector. A drying air flow rate above 0.6 m^3/min resulted in excessively high outlet air temperature which is undesirable. Even within this narrow range of drying air flow rate from 0.4 to 0.6 m^3/min, it was necessary to regulate the inlet drying temperature. A drying air flow rate of 0.6 m^3/min was too rapid for an inlet temperature of 150°C as the outlet temperature was very high while 0.4 m^3/min at 120°C was too low for a suitable and sufficient amount of products to be formed. The operational conditions were: Drying air flow rate (m^3/min)/inlet drying temperature (°C): 0.4/150, 0.5/150 and 0.5/120, 0.6/120.

Fig. 1 depicts the dissolution profiles of the spray-dried products obtained under the above-mentioned conditions while Table 1 lists the times taken for 50% release of the drug. The profiles shown in Fig. 1 are typical of all the products formed by spray drying under different conditions. The time for 50% drug release was then used as an index to compare differences in drug release rates. At both the inlet drying temperatures used, the dissolution $T_{50\%}$ was prolonged with a higher drying air flow rate. With the same inlet air temperature, an increase in residence time of the product in the drying chamber at a

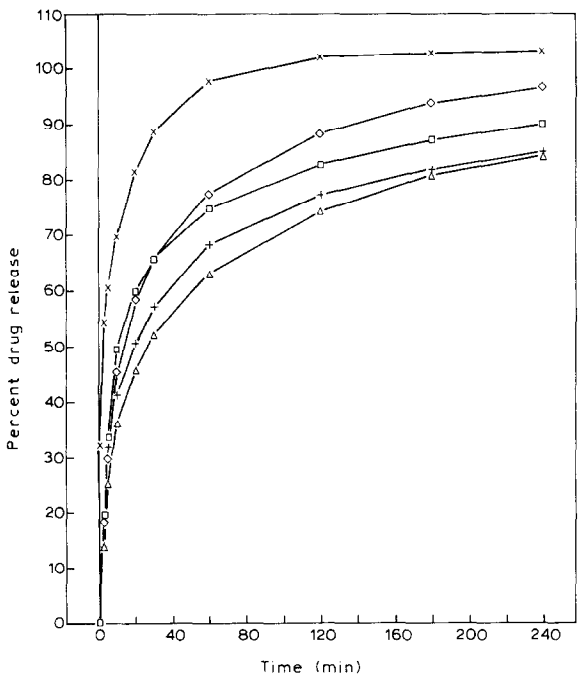

Fig. 1. Dissolution profiles of the spray-dried products obtained at varying air flow rates (m^3/min)/inlet drying temperatures (°C) [(□) 0.4/150, (+) 0.5/150, (◇) 0.5/120, (△) 0.6/120, (×) unsprayed theophylline].

lower air flow rate resulted in a longer drying period and therefore produced a spray-dried product with lower moisture content. There were two possible consequences: (a) a lower moisture content due to the more complete removal of water (Seagar, 1977) and (b) as more water became evaporated, more dissolved drug within the core was carried to the surface. With more drug particles exposed on the surface, the dissolution was consequently enhanced. However, the effect of lowering moisture content was only observed at a higher inlet temperature, i.e. 150°C (Table 1). This is because a drying temperature of 120°C was probably too low for sufficient drying. It has been postulated by Takeuchi et al. (1989) that the drying air flow rate can affect amorphism of the drug but such an effect was not apparent from preliminary results using the DSC, possibly due to the narrow range of drying air flow rates used.

The particles that were spray dried at a higher drying air flow rate were found to have improved flow properties as determined from Kawakita's constants and the calculated values of the Hausner ratio and Carr index (Table 1). It is advantageous to adopt 0.5 m^3/min as the air flow rate because of its operational suitability and the type of product being formed.

Since the effects of drying air rate were dependent on the interplay between inlet drying temperature and drying air flow rate, further spray-drying investigations were carried out at a flow rate of 0.5 m^3/min in order to evaluate the effect of the inlet air temperatures, 120, 130, 140 and 150 °C, on the spray-dried products. The dissolution $T_{50\%}$ from the products is depicted in Fig. 2 and Kawakita's constants, Hausner ratio and Carr index in Fig. 3.

From the above findings, it is seen that generally, the temperature of 140°C appeared to be ideal with the drying air flow rate of 0.5 m^3/min as the spray-dried product had a more prolonged drug release and fairly consistently good flowability. Therefore, in order to produce well-coated products with good flow, a high drying air flow rate with a compatible temperature is necessary.

TABLE 1

Dissolution $T_{50\%}$, moisture content and flow property measurements of spray-dried products prepared at different drying air flow rates

Drying air flow rate (m^3/min):	0.4	0.5	0.5	0.6
Inlet drying temperature (°C):	150	150	120	120
Dissolution $T_{50\%}$ (min) [a]	11.3	19.8	14.7	18.0
Moisture content (%)	5.17	7.13	7.95	7.21
Hausner ratio	1.52	1.49	1.59	1.59
Carr index	34.3	32.8	36.9	36.9
Kawakita's constants, a	0.26	0.22	0.25	0.24
$1/b$	34.0	21.5	25.8	23.5

[a] Time taken for 50% of drug to be released.

Spray rate of feed

Spray-dried products were prepared using different spray rates of feed, i.e. 7, 9, 12 and 15 ml/min. Dissolution studies were carried out on these products and the results are presented in Table 2. As the mean particle volume of the spray-dried products decreases, the rate of dissolution increases (Table 2). This could be attributed to the smaller particles having a greater

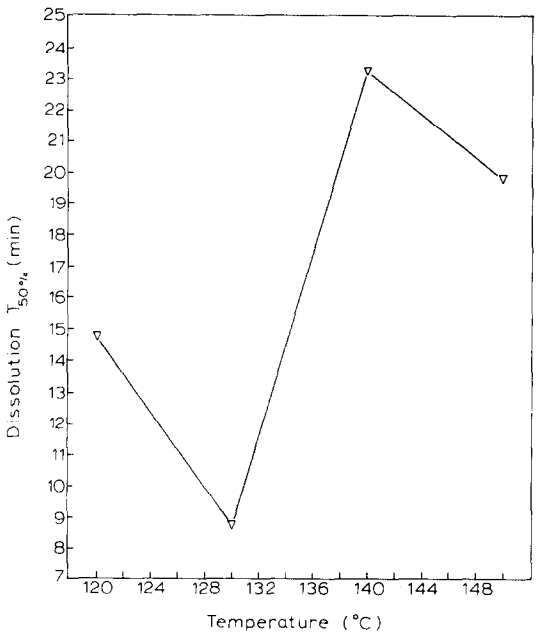

Fig. 2. Time for 50% drug release of the spray-dried particles produced at different inlet drying temperatures with an air flow rate of 0.5 m^3/min.

surface area. The particle volume of the spray-dried product prepared using a spray rate of 15 ml/min showed a slight increase in mean particle volume and a corresponding increase in the dissolution $T_{50\%}$ value. However, the marginal increase in particle volume could not account for the high dissolution $T_{50\%}$ value obtained. Agglomeration, in this case, may have played a part in delaying drug release. The phenomenon of mean particle volume decreasing with greater spray rate of feed is rather unusual. Theoretically, product size increases with higher feed rates. Masters (1985) described the products obtained from spray drying at varying feed rates. At low feed rates, the droplet sizes are of high homogeneity. At higher feed rates, the atomizing air cannot penetrate the thick liquid jets. Atomization is incomplete and a wide droplet-size distribution in the spray results. At high feed rates, therefore, it is important that the liquid feed should first form into thin sheets to assist liquid instability for effective air-liquid contact and breakdown of liquid into ligaments or individual droplets. Unless 'feed prefilming' takes place, ineffective atomization results, even at high air velocities. Bodmeier and Chang (1988), in using spray drying to prepare biodegradable polylactide microparticles, also encountered difficulty in the formation of droplets as a result of insufficient

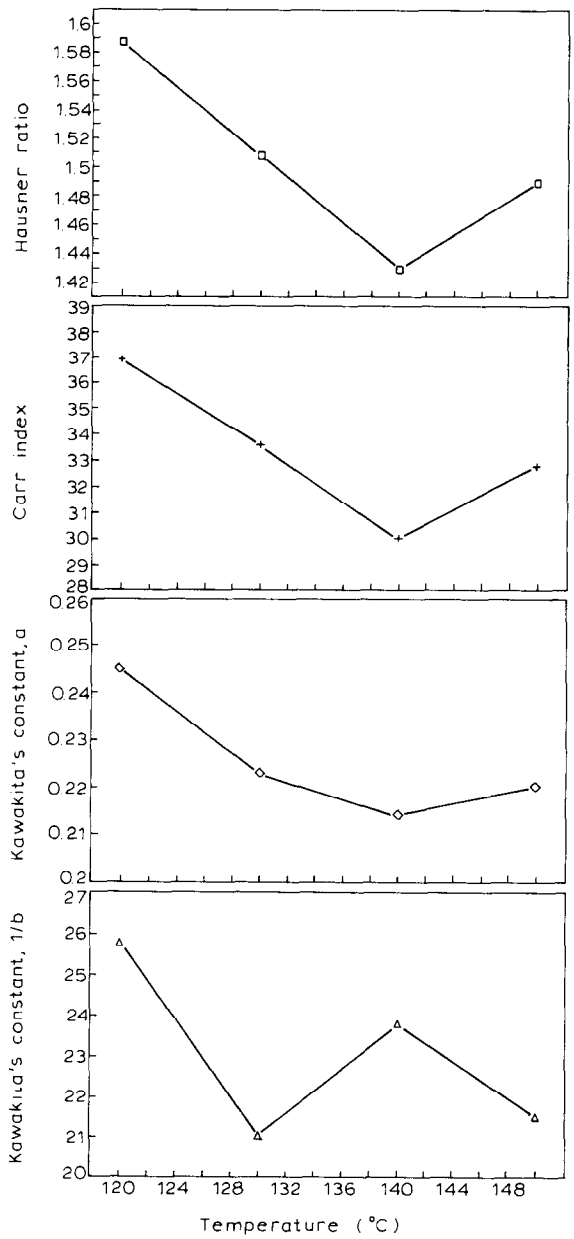

Fig. 3. Flow property constants determined for the spray-dried products formed at different inlet drying temperatures with an air flow of 0.5 m^3/min.

forces to break up the liquid filaments into droplets.

According to Seagar (1977), increasing feed spray rates will lead to a reduction in the outlet temperature and an increase in equilibrium solvent content or moisture level. However, although the outlet temperature was decreased, the moisture levels of the spray-dried products did not increase when higher feed rates were used (Table 2).

Ineffective atomization at higher spray rates led to the formation of large/irregular particles which were not completely dried when leaving the drying chamber. This resulted in the deposi-

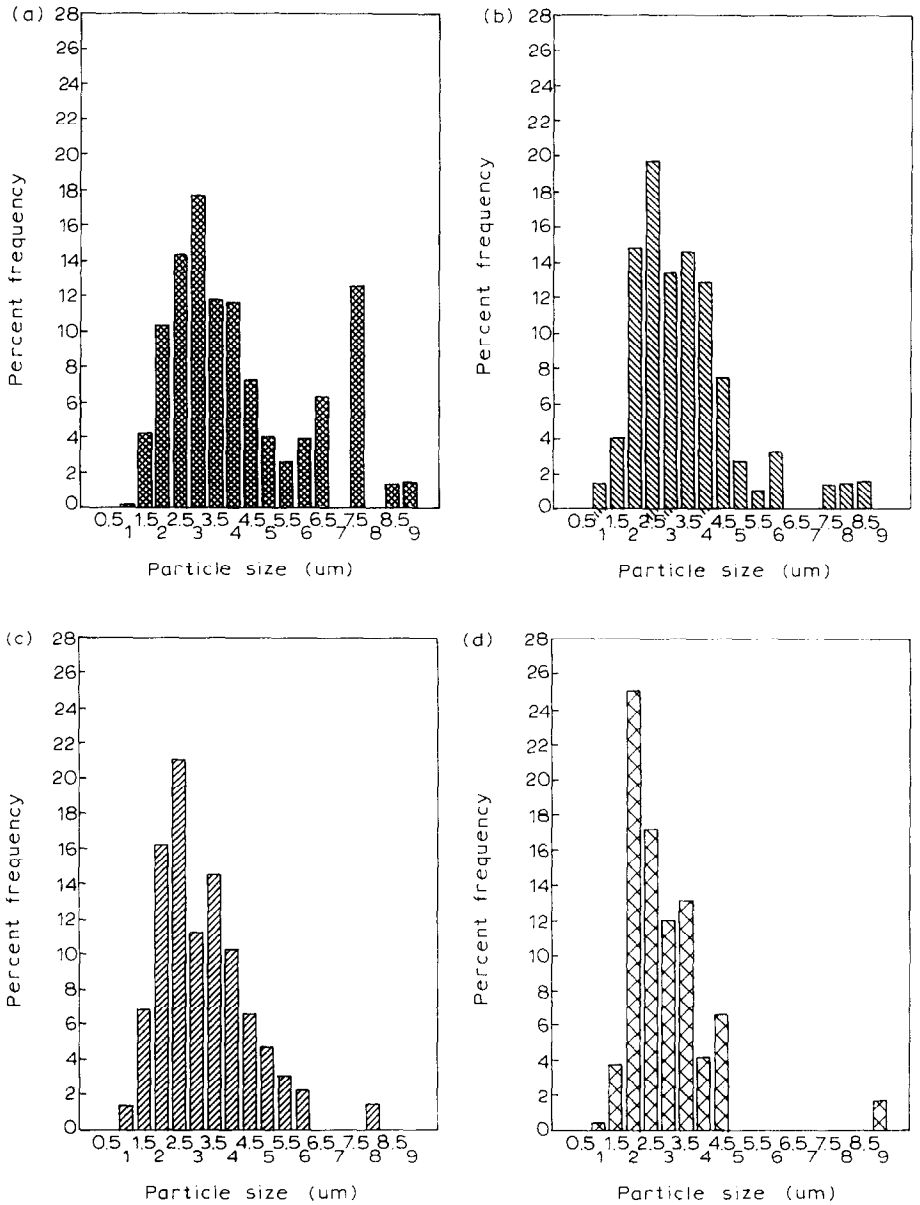

Fig. 4. Particle size distribution of the products obtained from feed spray rates of (a) 7, (b) 9, (c) 12 and (d) 15 ml/min.

tion of these large particles on the wall of the cyclone separator. The spray-dried particles gathered in the product collector were therefore those of smaller sizes which have lower moisture content. The wasted deposition of the large particles also explained the much lower yields obtained at the higher feed spray rates of 12 and 15 ml/min (Table 2). Deposition on the drying chamber and cyclone collector was caused by very coarse droplets being formed in the spray and incomplete atomization (Masters, 1985). It is observed from Fig. 4 that, at higher spray rates, a reduction in the number of large particles occurred. Fig. 5 shows photomicrographs of the spray-dried products obtained at spray rates of 7 and 15 ml/min. The spray-dried product produced at a spray rate of 15 ml/min was poorly formed (Fig. 5b).

The flow properties were found to be dependent on particle size (Table 2), the larger spray-dried particles having lower values of the Hausner ratio, Carr index and Kawakita's constants, a and $1/b$. The smaller particles produced at a spray rate of 15 ml/min tend to agglomerate, these agglomerates resulting in a slower drug release and this was substantiated by the data of dissolution $T_{50\%}$. During initial tapping of the product to determine Kawakita's constants, the agglomerates behaved as single aggregates, giving rise to low a and $1/b$ values. Prolonged tapping, to 1000 taps, broke down the aggregate into individual particles and therefore high values of the Hausner ratio and Carr index were obtained.

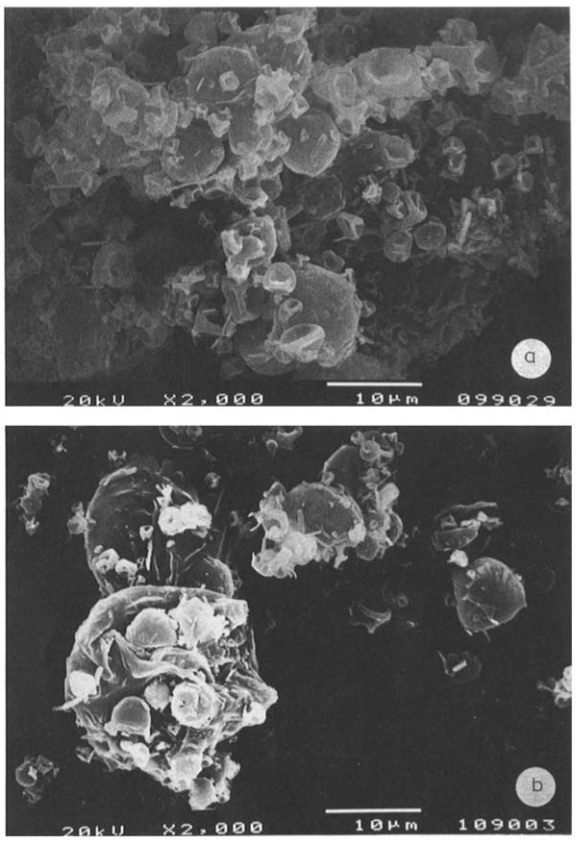

Fig. 5. Scanning electron photomicrographs showing the type of products developed through feed spray rates of (a) 7 and (b) 15 ml/min.

TABLE 2

Effect of feed spray rate on the properties of the spray-dried products

	Feed spray rate (ml/min)			
	7	9	12	15
Dissolution $T_{50\%}$ (min) [a]	27.6	23.1	17.7	31.7
Mean particle volume (μm^3)	12.8	8.6	7.5	8.0
Moisture content (%)	5.8	6.5	4.8	4.8
Outlet temperature (°C)	88	82	78	71
Yield of products (%)	40	46	34	27
Hausner ratio	1.49	1.48	1.53	1.52
Carr index	33.5	32.5	34.5	34.3
Kawakita's constants, a	0.22	0.27	0.29	0.24
$1/b$	24.9	30.2	31.5	21.5

[a] Time taken for 50% of drug to be released.

These results show that there is a limit to which the size of the particles can be increased without compromising the formation of well-coated products. To produce large well-formed microcapsules, increasing the feed spray rate is not recommended unless effective and complete atomization can be ensured. However, spray rates which are too low have the disadvantages of low efficiency with longer operation time and a high outlet temperature which may affect the exhaust tubings.

Atomizing pressure

The air velocity controls the atomizing pressure required to break down the liquid feed into

droplets. The air pressures evaluated were 0.5, 1, 1.5 and 2 kgf/cm^2. A reduction in air pressure results in an increase in the spray angle as long as the maximum angle has not been attained (Masters, 1985). The wider spray angle caused deposition of the droplets on the walls of the drying chamber observed during the process of spray drying. The yield obtained was thus much lower at a low atomizing pressure (Table 3).

The mean particle volumes of the products spray dried at an atomizing pressure of 0.5 and 2 kgf/cm^2 were 16.68 and 5.99 μm^3, respectively. Comparing the two volumes, there was a reduction of almost two-thirds in volume for the products obtained using higher atomizing pressure. Mean droplet size decreases with increase in air velocity as more energy is available for atomization. The smaller particles would account for the decrease in dissolution $T_{50\%}$ (Fig. 6) because of a comparatively greater surface area exposed to the dissolution medium during dissolution studies.

The flowability of these spray-dried particles (Table 3) shows the same trend in the Hausner ratio, Carr index and Kawakita's constants, a and $1/b$. Generally, the spray-dried product obtained at an atomizing pressure of 1 kgf/cm^2 appeared to have greater compactibility. The low values obtained with particles formed at a pressure of 2 kgf/cm^2 could be due to agglomerates of the small particles behaving as a single entity. An atomizing pressure of 1 kgf/cm^2 was therefore considered as the ideal pressure after evaluation of the results from the dissolution and flow parameters.

TABLE 3

Yield and flow property measurements of the spray-dried products formed at different atomizing pressures

	Atomizing pressure (kgf/cm^2)			
	0.5	1	1.5	2
Yield of products (%)	26	43	42	51
Hausner ratio	1.47	1.43	1.50	1.43
Carr index	31.9	29.9	33.2	30.1
Kawakita's constants, a	0.24	0.22	0.26	0.20
$1/b$	24.9	22.5	27.4	19.4

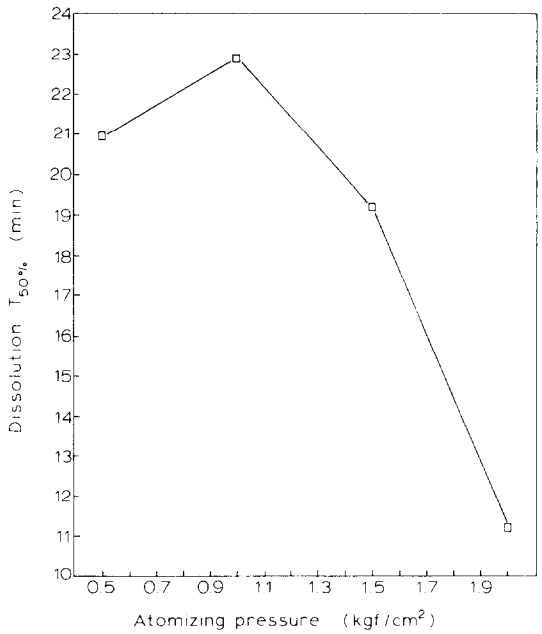

Fig. 6. Dissolution $T_{50\%}$ of the spray-dried products obtained with different atomizing pressures.

The present findings show that the spray-drying technique can be a very useful method for coating drug materials. The simplicity of the process and the possible use of aqueous solvents without the need for an additional drying step give it an added advantage over other microencapsulation techniques. In adopting this method, it is preferable to employ higher drying air flow rates as this results in products with improved flowability and slower drug release. It should be noted that an increase in feed rate need not result in a corresponding increase in product size nor moisture content as theoretically predicted. These factors are related to effectiveness in atomization and affect product yield. Atomizing pressure changes only affected the product size which led to changes in dissolution and flow properties.

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